50. The method of claim 48 or 49 wherein said allergic disorder is selected from the group consisting of allergic rhinitis, allergic contact dermatitis, anaphylactic reactions, asthma, and bronchitis.

51. The method of any one of claim 48, 49 and 50 wherein the antibody is administered parenterally.

52. The method of claim 51 wherein parenterally includes subcutaneous, intravascular, intravenous, rectal, vaginal and intraperitoneal administration.

53. The method of claim 52 wherein the antibody is administered by subcutaneous administration.

54. The method of any one of claims 48-53 wherein the antibody is lyophilised for storage and reconstituted prior to administration.

REMARKS

Entry of the foregoing amendments, reconsideration and re-examination of the subject application, as amended, pursuant to and consistent with 37 C.F.R. §1.112, and in light of the remarks which follow, are respectfully requested.

By the present amendments, the specification has been amended to correct the numbering of certain Sequence ID NOs. in the specification. Essentially, SEQ ID NOs.: 1-8 correspond to nucleic acid or amino acid sequences for primate anti-human CD23 antibody variable domains whereas SEQ ID NOs: 9-39 are primers. This is clear from the sequence listing and the as-filed disclosure.

Also, new claims 48-59 are added which directly correspond to subject matter for which the Examiner indicated was enabled by the teachings of this application. New claims 48 and 49 almost verbatim claim what the Examiner states at page 2 of the Office Action is enabled. Claims 50-54 are directed to treatment of specific allergic disorders finding support at pages 81-84 of the specification, specific modes of administration finding support at page 85, lines 12-14, and provide for the antibody to be lyophilised and reconstituted prior to administration (find support at page 94,

last full paragraph). Applicants advise that the subject anti-CD23 antibodies are now in clinical trials for treatment of allergic asthma.

Turning now to the Office Action, Claims 38-46 stand rejected under 35 U.S.C. §112 first paragraph based on asserted lack of enablement. This rejection is respectfully traversed.

Essentially, the Examiner's position is that the specification only enables treatment of allergic disorders using the subject antibodies and does not adequately teach how to use the subject antibodies for treating other (non-allergic) IgE related diseases, particularly autoimmune, inflammatory and transplant conditions.

The enablement rejection is respectfully traversed on the basis that it is unsupported by convincing scientific reasoning as to why the invention will not work as claimed, absent undue experimentation. With respect thereto, the Examiner is respectfully reminded that the claims under examination merely require that the administered anti-CD23 antibody inhibit IgE production in patients in need of such inhibition. The fact that several antibodies according to the invention possess this activity is evidenced by the results contained in the subject application. This has been demonstrated by the results with the exemplified anti-human CD23 antibodies both in vitro assays (examples 1 and 2) and in vivo (in SCID mice, an accepted animal model for study of the human immune system, note Example 3 of the subject application).

With respect to the alleged failure to teach how "to use" the invention, the subject application contains substantial disclosure relating to preferred dosage formulations, dosage regimens, modes of administration, and means for storing and formulating the subject antibodies prior to administration. Also, the subject application provides substantial information on how to make recombinant anti-human CD23 antibodies according to the invention. Still further, the specification identifies a number of diseases wherein inhibition of IgE production is therapeutically desirable.

Accordingly, it is unclear what information the specification "lacks" to teach one of skill in the art how to practice the invention. Essentially, as the subject application adequately demonstrates that anti-human CD23 antibodies according to the invention, i.e., those that posses human gamma 1 constant domains, possess substantial IgE inhibitory actively, indeed unexpectedly enhanced IgE-inhibitory

activity improved vis-à-vis antibodies possessing different constant or no constant domains.

While it is believed that the subject application adequately enables the claimed invention, in further support of the efficacy of the claimed invention, Applicants enclose herewith Busse et al., J. Allergy and Clin. Immunol. 107(2): 354 (2001) and Nakamura et al., Int. J. Immunopharmacology 22:131-141 (2000) both of which articles substantiate that antibodies according to the invention effectively inhibit IgE production. There is, moreover, no basis to believe that these results are affected by the species of origin of the antibody variable region. In fact, the Nakamura article, consistent with the scope of the claims, makes clear that IgE inhibition is functionally dependent on the immunoglobulin Fc domain (based on the fact that a gamma 4 constant domain containing anti-human CD23 antibody (p5E8G4)) and a $F(ab)_2$ fragment of p5E8G1 did not inhibit IgE production comparable to p5E8G1 (containing a human gamma 1 constant domain).

It is noted that the Busse (Id) abstract teaches that antibodies according to the invention inhibit IgE levels in human patients, in a dose-dependent manner, with no significant adverse events relative to placebo-treated patients. Moreover, while the treated patients had allergic asthma (an allergic disorder), the Examiner has not provided any convincing reasons as to why similar effects (upon administration, the anti-CD23 antibody is safe and effective, i.e., results in IgE inhibition) will not be achieved in patients with other allergic diseases as well as non-allergic diseases.

Further, with respect to claims 48-59, these claims certainly should be free of the §112 enablement rejection as these claims are directed to subject matter which the Examiner has acknowledged is enabled by the subject application.

Also, the fact that the Merck manual does not teach any method or treating the two-mentioned autoimmune i.e., ankylosing, spondylitis and rhematoid arthritis is irrelevant as the claims are not directed to treating or preventing autoimmune diseases or inflammatory diseases. By contrast, the claims are directed to inhibiting IgE levels in patients in need of such inhibition, which includes patients that have an autoimmune or inflammatory disease. Again, as it has been demonstrated that the subject antibodies possess IgE inhibitory activity, there is no reason for disputing the efficacy of the invention as claimed.

Based on the foregoing, withdrawal of the §112 first paragraph rejection in its entirety is earnestly requested, especially as there is no evidence or reason to believe that other IgG1 anti-human anti-CD23 antibodies will not yield similar results in human patients having conditions wherein inhibition of IgE is therapeutically beneficial.

Claims 38-46 also stand rejected based on lack of written description. This rejection is respectfully traversed for the same reasons as the enablement rejection, supra.

Also, Applicants respectfully submit that the objection to "primate antigen binding portion" is without merit as this simply that the recitation clearly means a portion of the antibody that facilitates binding to antigen (CD23). Quite clearly those skilled in the art are well aware as to the portion of antibodies that are involved in antigen binding.

With respect to the Examiner's question relating to what sequences are primers and which are variable sequences, the specification has been amended to clarify that SEQ ID NOS.: 9-39 (contained in Tables 1-4) correspond to primers. By contrast, SEQ ID NOS: 1-8 correspond to primate variable heavy and light sequences which were used to construct the exemplified anti-human CD23 IgG1 antibodies. (Note the amendments to page 50 with respect to SEQ ID NOS.) This fact is clear e.g., from the SEQUENCE LISTING submitted with this application.

Further, with respect to the Examiner's indication that the specification does not provide written description support for treating transplant rejection, autoimmune and inflammatory diseases, he Examiner is again respectfully reminded that methods for effecting inhibition of IgE's are claimed, which finds substantial written description support in the specification, as does IgE inhibition in the context of treating patients with autoimmune and inflammatory diseases. Indeed, this is clearly disclosed in the specification e.g., at pages 81-84 wherein a large number of such diseases are expressly identified. Also, the specification clearly describes how such antibodies are prepared, how they should be administered in order to inhibit IgE, and what are preferred dosages that should be administered for therapy. In fact, it is unclear how the written description requirement could be violated given the extensive

teachings in this application regarding the use of the subject antibodies for inhibiting IgE in patients in need of such treatment.

Based on the foregoing, withdrawal of the §112 written description rejection is respectfully requested.

Claims 39 and 41 stand rejected under 35 U.S.C. §112 second paragraph because the word "portion" is alleged to be ambiguous. The Examiner indicates that this could be construed to be a single amino acid. However, the position of the Examiner is believed to be unsustainable. As these claims require an "antigen binding portion" this cannot be a single amino acid but rather would clearly require that a portion of the antibody that is sufficient for antigen (CD23) binding, i.e., the variable region of a primate or rodent antibody. Withdrawal of this rejection is respectfully believed to be in order.

Claims 38, 40-45 and 47 stand rejected under 35 U.S.C. §102 (a) as assertedly being anticipated by WO 96/12741 in view of Saxon et al. This rejection is respectfully traversed on the basis that it is legally unsustainable.

As previously noted, the primary reference provides a large listing of potential CD23 antagonists including antibodies, antibody fragments, small molecules, and peptides and uses thereof, including treatment of allergic disorders. Among the potential antagonists are anti-human CD23 antibodies which may comprise different types of human constant and other species domains including human gamma 1, gamma 2, gamma 3 and gamma 4. However, as previously argued, no anti-human CD23 antibodies are exemplified which comprise a human constant domain, much less a human gamma 1 constant domain. Absent such exemplification in the reference, the rejection properly should have been made under §103, obviousness grounds and not anticipation grounds. Particularly, there is no specific teaching relating to the administration of an anti-human CD23 IgG1 antibody to inhibit IgE in a patient in need of such inhibition unless different teachings of the reference are combined and chosen in lieu of other teachings. Essentially, the supposed "anticipation" rejection requires a picking and choosing among many different possibilities in the reference with no specific recognition that IgG1 antibodies would be in any way favored over other types of antibodies or antibody fragments.

This clearly violates the anticipation requirement which requires that the prior art should clearly teach all elements of the claimed invention. The Saxon reference does not save the rejection. It is acknowledged that Saxon teaches that anti-CD23 antibodies may inhibit IgE production. However, the reference also does not establish or suggest that it would have been reasonably expected as of the date of invention that the subject IgG1 anti-human CD23 antibodies would possess advantageous properties vis-à-vis other types of anti-human CD23 antibodies such that one skilled in the art would have been motivated to select such antibodies for therapy.

In fact, based on the teachings of the prior art, it would have been more preferred to administer anti-CD23 antibody fragments since the expectation would have been that they would be effective (inhibit IgE) and be less immunogenic because of their smaller size. This would be a prevalent concern, especially in the context of treating an allergic patient.

With respect thereto, the Examiner again seems to fail to take into account the unexpected results achieved by the use of antibodies that possess IgG1 constant domains. This fact is supported by the data in the subject application which compares the IgE inhibitory activity of antibodies having the same antigen-binding portion but different constant regions or no constant regions. As evidenced by the IgE inhibitory activity achieved by these different species (see Examples in the application), it is clear that the subject IgG1 antibodies exhibited demonstrably better IgE inhibitory activity relative to antibodies containing different constant regions. These enhanced results are further supported by Nakamura et al. Int. J. Immunopharacol. 22:131-141(2000). This reference clearly teaches that anti-CD23 antibodies which possess specific types of Fc domains (IgG1) inhibit IgE production differently (better) than antibodies containing different Fc domains and further conclude that this enhancement likely correlates to the cross-linking of CD23 to an IgG receptor.

Therefore, based on the foregoing, withdrawal of the rejection based on WO 96/12741 in view of Saxon is respectfully requested.

Claims 38-39 and 43 also stand rejected under 35 U.S.C. §103(a) as being unpatentable over WO 96/12741 in view of Saxon et al. and U.S. Patent 5,658, 570.

This rejection is respectfully traversed for the same reasons as the above rejection based on these references. The '570 patent is again cited based on its

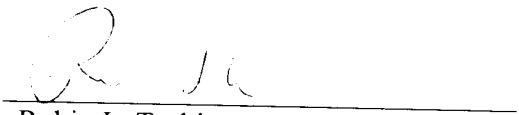
disclosure relating to the production of primatized antibodies. This is acknowledged to have been known as of the date of invention. However, this does not render the claims unpatentable absent any disclosure or expectation regarding the enhanced IgE inhibiting properties of primatized anti-CD23 antibodies possessing human gamma 1 constant domains. Likewise, the WO 96/12741 and Saxon et al references do not provide this teaching.

Therefore, based on the following withdrawal of the §103 rejection of claims 38-39 and 43 based on WO 96/12741 in view of Saxon et al. and U.S. Patent 5,658,570 is respectfully requested.

Based on the foregoing, this application is believed to be in condition for allowance. A Notice to that effect is respectfully solicited.

Respectfully submitted,

PILLSBURY WINTHROP LLP



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APPENDIX

IN THE SPECIFICATION

Page 47, first paragraph

The first PCR amplification of the light chain of the light chain variable region from the cDNA of the primate monoclonal antibody 6G5 showed bands which were consistent in situ with the lambda light chain variable region. These bands appeared in all reactions using the three different early leader sequence primers. (See Tables 1-3.) [SEQ ID NOS: ~~5-21~~-9-25] However, the PCR product obtained using primer 745 (Family 2) was considered more specific because of the relatively greater intensity of the PCR product band.

Page 49, last paragraph

To confirm this was an immunoglobulin light chain variable domain, sequencing was done using the Sequenase 7-Deaza –dGTP DNA Sequencing Kit (USB catalog # 70990) with sequencing primers 607 and GE 108. (See Sequencing Primers in Table 4.) [SEQ ID NOS.: ~~5-21~~-26-35]

Page 50, first paragraph

A second independent PCR amplification of the light chain from cDNA of primate monoclonal antibody 6G5 was effected using a 5' primer early leader sequence of lambda light chain family 2 (primer 745) and the 3' J region primer 926. (See Primers for PCR of the lambda light chain variable domain of 6G5 in Tables 1-3.) [SEQ ID NOS.: ~~5-21~~-9-25] The isolated PCR product (see technique above) was cloned into TA vector by using the Original TA Cloning (Kit (Invitrogen Catalog # K2000-01). (The isolated mniprep DNA (see technique above) was examined under agarose gel electrophoresis after digestion with EcoR I restriction endonuclease. The resultant PCR product comprised in the TA vector was then sequenced (as described previously) using Sp6 and M13 (-40) forward primers (See Sequencing primers in Table 4). [SEQ ID NOS.: ~~22-31~~-26-35] The resultant light chain sequence was identical to that of light chain from the fist PCR. This entire sequence [SEQ ID NO.: 1] of the light chain variable domain of primate monoclonal anti-human CD23 antibody 6G5 is presented below.

Page 52, last paragraph – Page 53, first paragraph

The first PCR amplification of the heavy chain variable domain from cDNA of primate monoclonal antibody 6G5 was performed by using the set of early leader sequence primers described supra and the 3' J region primer GE244. These primers are in Tables 1-3 [SEQ ID NOS.: ~~5-21~~-9-25] infra. This reaction resulted in a 350 base PCR product. This 350 base product (purified as described supra), was digested with Nhe I and Sal I, and ligated into N5LG1 and digested with the same endonucleases in the first PCR amplification. The resultant ligation mixture was transformed into host cells using the same techniques for cloning the light chain. Plasmid N5LG1 containing the 350 base PCR product was then isolated and sequenced (using sequencing primers 266 and 268). (These Sequencing primers are set forth in Table 4.) [SEQ ID NOS.: ~~22-31~~-26-35]

Page 54, second paragraph

A fourth independent PCR was performed using the same primers as the third PCR amplification. This resulted in a PCR product which was isolated and cloned into the TA vector as described previously. The sequence of the fourth independent PCR product was found to be identical to that obtained in the third PCR amplification. This sequence, [SEQ ID NOS.:~~-23~~-4] which comprises the heavy chain variable domain of primate monoclonal anti-human CD23 antibody 6G5, is presented below.

Page 57, last paragraph – Page 58 continuation of last paragraph on Page 57

The first PCR reaction of the light chain variable domain from 5E8 cDNA was carried out using a set of kappa early leader sequence primers and the 3' J region primer GE204. (See primers for PCR of the kappa light chain variable domain of 5E8 in Tables 1-3). [SEQ ID NO.: ~~5-21~~-9-25] A 420 base PCR product was obtained. The isolated 420 base PCR product was digested with Bg1 II and BsiW I restriction endonucleases, cloned into the mammalian expression vector N5KG4P and sequenced using GE108 and 377 primers (which are contained in Table 4). [SEQ ID NO.: ~~22-31~~-26-35] The mammalian expression vector N5KG4P is identical to the vector N5LG4P except it contains the human kappa light chain constant region is place of the human lambda light chain constant region. Sequencing of this 420 polynucleotide DNA revealed that it contains the entire kappa light chain variable domain.

Page 58, last paragraph

A second independent PCR of the light chain variable region was performed using the 5' family 1 primer GE201 and the 3' primer Ge204. (See primers for PCR of the kappa light chain variable domain of 5E8 in Tables 1-3). [SEQ ID NO.:~~5-21~~ 9-25] The isolated PCR product was cloned into the TA vector (using methods previously described) and sequenced using Sp6 and T7 promoter primers. Sequencing revealed that this PCR product was identical to that obtained from the first PCR. The entire sequence [SEQ ID NO.: 3] of the light chain variable domain of primate monoclonal anti-human CD23 antibody 5E8 is presented below.

Page 60, last paragraph – Page 61, first paragraph

The first PCR of the heavy chain variable domain of 5E8 was performed using a set 5' early leader heavy chain sequence primers and the 3' primer GE210. (See primers for PCR of the heavy chain variable domain of 6G5 and 5E8 in Table 1). [SEQ ID NO.:~~5~~9-13] A 420 base PCR product appeared in the family 3 primer reaction. The PCR product was purified and then digested with Nhe and Sal I and cloned into the mammalian expression vector N5KG4P vector (as described previously). The PCR product was sequenced using the 268 and 928 primers. (See sequencing primers in Table 4.) [SEQ ID NOS.:~~22-31~~26-35]

Page 61, second paragraph

A second independent PCR of the heavy chain variable domain of 5E8 was performed using the family 3 5' primer GE207 and the 3' primer GE210. (See primers for PCR of the heavy chain variable domain of 6G5 and 5E8 in Tables 1-3). [SEQ ID NOS.: ~~5-21~~9-25] The isolated PCR product was cloned into a TA vector using the same techniques previously described and sequenced by using Sp6 and T7 primers. Sequencing revealed that the TAC at codon 91 had been changed into TGC.

In order to determine the appropriate codon at 91, a third independent PCR was performed using the same primers as the second PCR (see above). The PCR product was again cloned into a TA vector and sequenced using Sp6 and T7 primers. The sequence was found to be identical to the heavy chain variable sequence obtained in the first PCR. Therefore, the TGC at position 91 in the second independent PCR product is apparently the result of an error introduced during PCR. This entire

sequence [SEQ ID NO.: 4] of the heavy chain variable domain of primate monoclonal anti-human CD23 antibody 5E8 is presented below. [SEQ ID NOS.: 7-8]

Page 65, second, third and last paragraphs

A first PCR was done using N5KG4P + 5E8 as a template and a 3' primer (corresponding to codon 71 to 79) and which contains a mutation at codon 75 (AAC changed to AAG, Primer MB1654, and a 5' primer at the beginning of the leader sequence (Primer MN1650). (See PCR Primers Used for the Generation of a Glycosylation Mutant of the Heavy Chain Variable Region 5E8 set fourth in Table 5). [SEQ ID NOS.: ~~32-35~~36-39]

A second PCR was performed on the same template by using a 5' primer (corresponding to codon 71 to 79) containing the same mutation (Primer MB1653) and a 3' primer from the end of framework 4 (Primer MB1651) (See PCR Primers Used for the Generation of a glycosylation Mutant of the Heavy Chain Variable Region of 5E8 in Table 5.) [SEQ ID NOS.: ~~32-35~~36-39]

These two PCR products were isolated and mixed in equal molar ratios. A third independent PCR was then carried out by using the mixture of the first and second first PCR products as a template with a 5' primer used in the first PCR (MB1650) and a 3' primer used in the second PCR (MB1651). (See PCR Primers Used for the Generation of a Glycosylation Mutant of the Heavy Chain Variable Region in Table 5.) [SEQ ID NOS.: ~~32-35~~36-39] The PCR product obtained in third PCR was found to contain the heavy variable domain coding region of 5E8 wherein the asparagine 75 had been changed to lysine.